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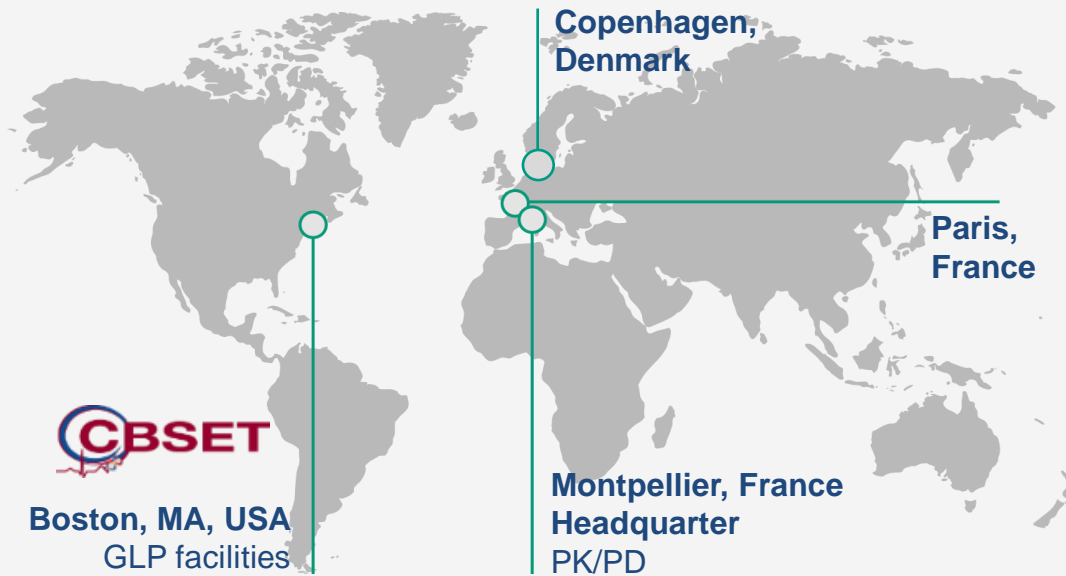
Montpellier
www.cilcare.com

NOTRE ACTIVITÉ

CILcare est une CRO spécialisée dans l'audition et leader mondial dans le domaine.
Implantée en France, aux Etats-Unis, et au Danemark, la société accompagne les industries pharmaceutiques, nutraceutiques, biotechs et medtechs dans le développement de nouvelles thérapies pour prévenir et traiter la surdité, les acouphènes et les otites.

CILcare is the world leading CRO in Hearing Disorders

Established in France, US, & Denmark, CILcare operates worldwide since its inception in 2014.

+120 studies

+60 clients

2 labs

- Pharmaceutical
- Nutraceutical
- Veterinary
- Medical devices

Copenhagen, Denmark

Paris, France

CBSET

Boston, MA, USA
GLP facilities

Montpellier, France
Headquarter
PK/PD

> 20 years of experience in pharmaceutical development
*Track record of drug candidates which succeed to market approval*

CILcare's US partner: CBSET

- Translational research institute providing high quality collaborative studies
  - Full preclinical programs + specific study design
  - AAALAC-accredited, **GLP-compliant** analyses
  - Board Certified Clinical Veterinarians & Veterinary Pathologists
  - Multispecies housing
- Founders from MIT, Brigham & Women's Hospital, Charles River Laboratories
- Founded in 2006, Headquartered in Lexington, MA

Peter Markham
CEO & Co-founder
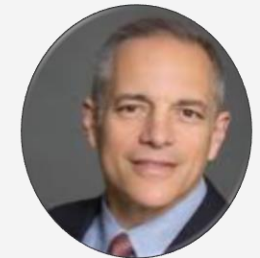
Elazer Edelman, Chairman
Director, Harvard-MIT
Biomedical Engineering Center

40,000 ft² purpose-built facilitiy with 2 state-of-the art surgical suites with high resolution imaging capabilities

Hearing disorders are dramatically increasing:
In 2050, 1 in 10 people will have hearing loss
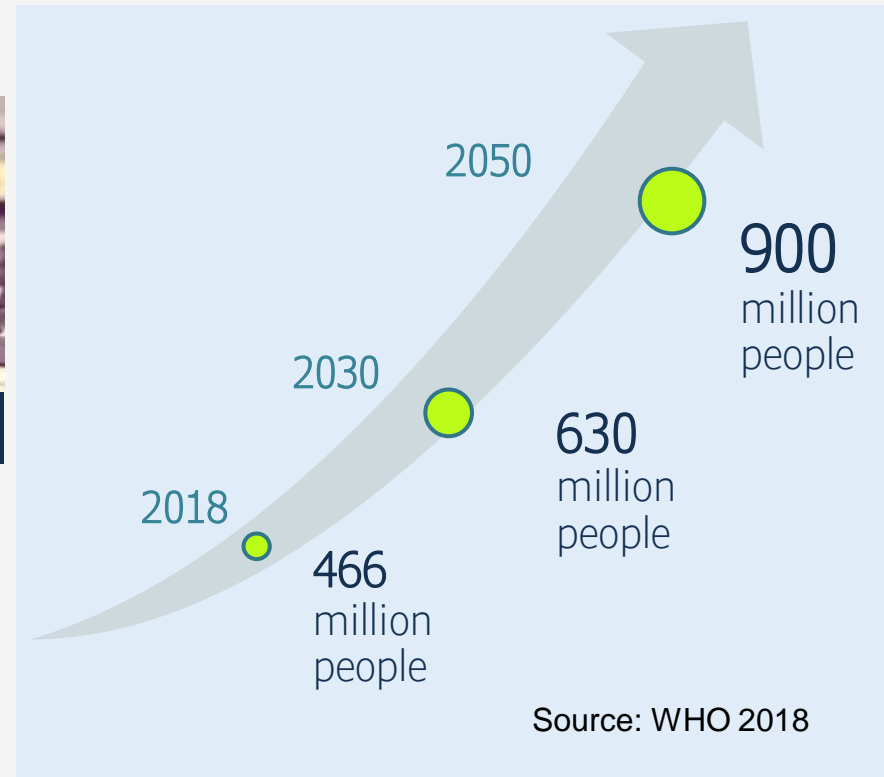
Aging populations

Noise exposure

Ototoxic drug intake

Infections

2050

2030

2018

900 million people

630 million people

466 million people

Source: WHO 2018

« The number of Americans living with **hearing loss** exceeds those living with **Parkinson's**, **Epilepsy**, **Alzheimer's**, and **Diabetes** combined"

Hearing Health Foundation

AFSSI

Association Française des Sociétés de Services et d'Innovation

www.afssi.fr

There are currently no approved therapeutics for hearing loss & tinnitus

Existing solutions are limited, expensive, stigmatizing and poorly reimbursed
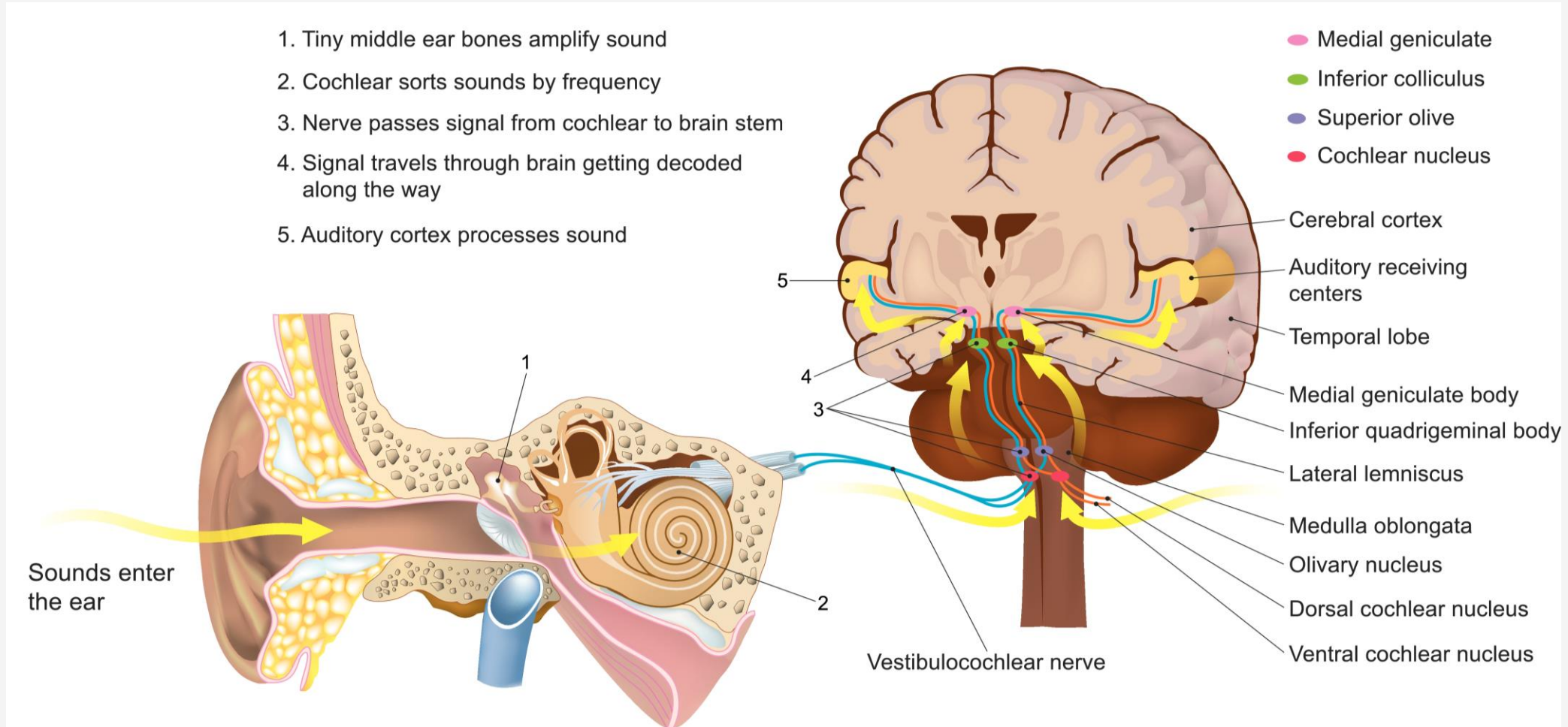
Hearing aids

Cochlear implants

Patients, physicians, and insurance companies are waiting for effective pharmacological solutions to prevent and treat ear disorders

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Inner ear: a tiny & complex organ connected to the brain, requiring a strong expertise and years of experience of R&D
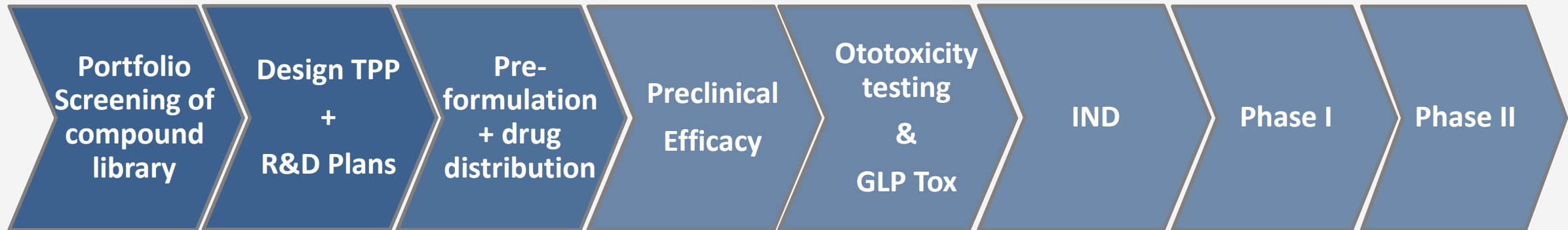
CILcare:

Your one-stop partner for external innovation in Hearing Disorders

We coordinate, manage and monitor the entire development chain:

| Portfolio Screening of compound library | Design TPP + R&D Plans | Pre-formulation + drug distribution | Preclinical Efficacy | Ototoxicity testing & GLP Tox | IND | Phase I | Phase II |

Therapeutic compounds

Gene & cell therapy

Cochlear implants

Drug Delivery Systems

AFSSI — Sciences de la Vie

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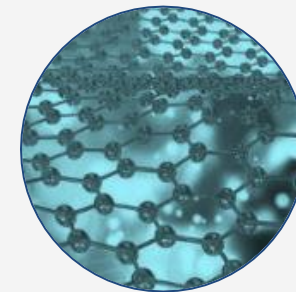
CILcare has created unique translational models for hearing disorders

PRESBYCUSIS	TINNITUS	HEARING LOSS	OTOTOXICITY	GENETIC DEAFNESS	OTITIS MEDIA
• Age-related hearing loss	• Salicylate-induced tinnitus • Noise-induced tinnitus	• Noise-induced hearing loss	• Drug-induced hearing loss	• Gene therapy	• Otitis media
MICE SAMP8	**RATS** Long Evans	**RATS** Wistar **GUINEA PIGS** Hartley	**RATS** Wistar **MICE** CBA	**RODENTS** **CHINCHILLAS** **MINI PIGS** **SHEEP**	**CHINCHILLAS** Bastard F1N1
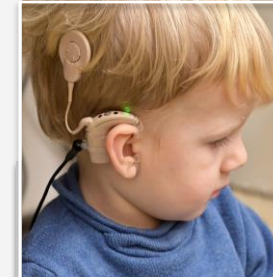
Hearing loss efficacy models

Model	HL induction	Species	In vivo phase duration	Read-outs
Drug	Cisplatin Gentamicin	Rats	4 days 15 to 22 days	• ABR, Wave I analysis • DPOAE • Cochleogram, Ribbon synapse, SGN • RNA & protein arrays
Noise	Acoustic trauma → Permanent or transitory threshold shift	Rats, mice Guinea pigs	10 to 21 days	
Age	Use of a specific strain with remarkable age-related deterioration	SAMP8 mice	14 weeks	

ABR
(Auditory Brainstem Response)

Baseline (n=50)
T+3days (n=50)
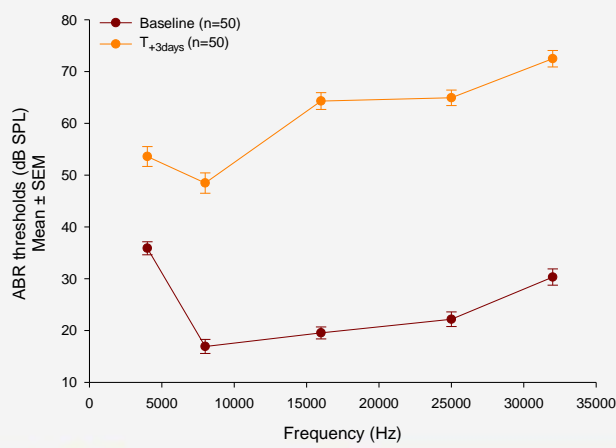
DPOAE
(Distorsion Product Otoacoustic Emissions)

Baseline (n=12)
D7 (n=12)
D14 (n=10-12)
D21 (n=10-12)
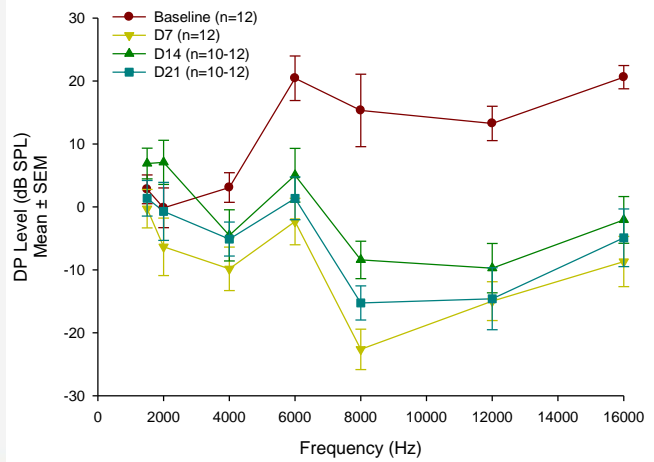
Cochleogram
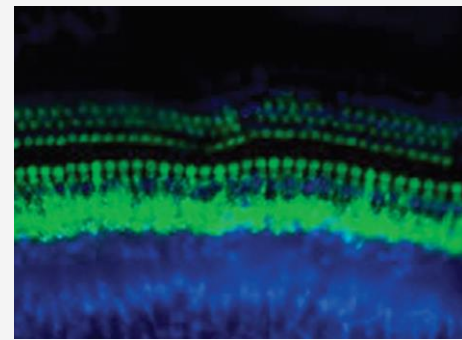
Hair cell counting

Imaging (SEM)

Analysis of hair cell morphology

Tinnitus efficacy models

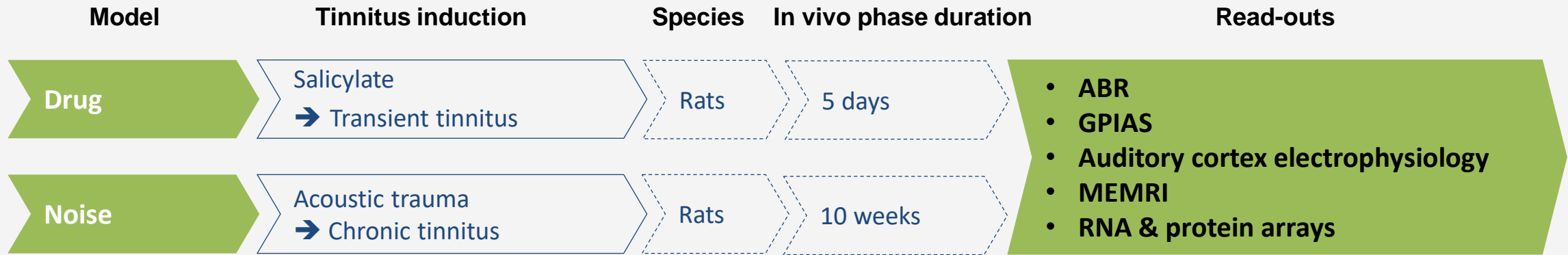| Model	Tinnitus induction	Species	In vivo phase duration	Read-outs
Drug	Salicylate → Transient tinnitus	Rats	5 days	• **ABR**
Noise	Acoustic trauma → Chronic tinnitus	Rats	10 weeks	• **GPIAS** • **Auditory cortex electrophysiology** • **MEMRI** • **RNA & protein arrays**

GPIAS
(Gap Prepulse Inhibition of Acoustic Startle)

Silent Gap in Background

Normally Inhibited Startle Reflex

** Tinnitus Partially Fills Gap

** Less Inhibition of Startle Reflex

Legend:
- Sham baseline
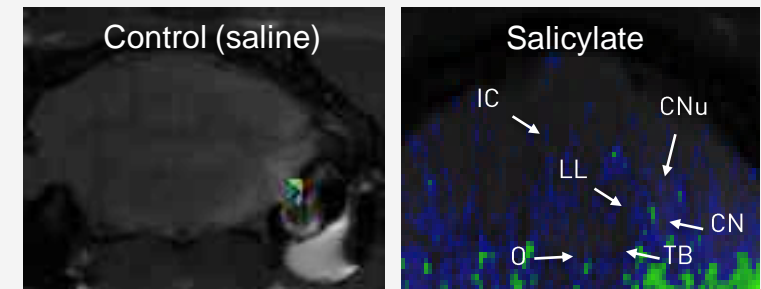- Acoustic trauma baseline
- Sham 30 days
- Acoustic trauma 30 days

y-axis: (NoGap-Gap) / NoGap x 100 Gap Inhibition (%) Mean ± SEM

x-axis: BBN, 10kH$_2$, 12kH$_2$, 16kH$_2$, 24kH$_2$

ns   ns   *   *   *

MEMRI

Control (saline)

Salicylate

IC, CNu, LL, CN, O, TB
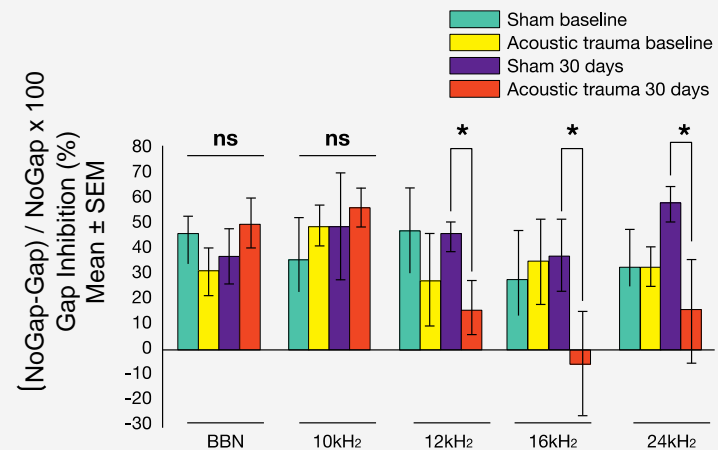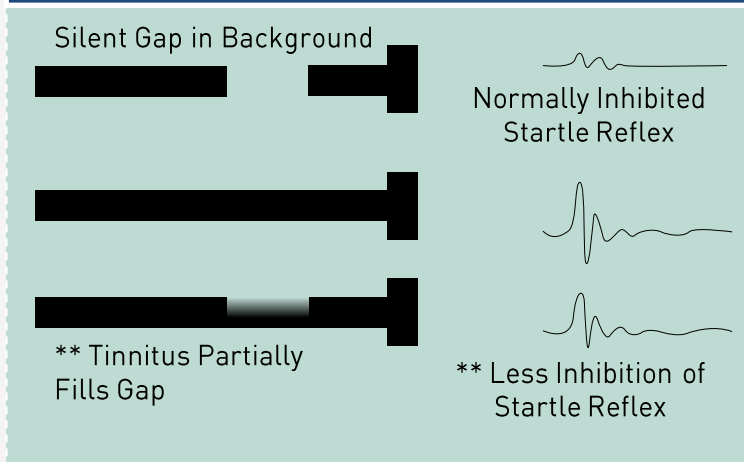
Auditory brain stucture imaging

Otitis models

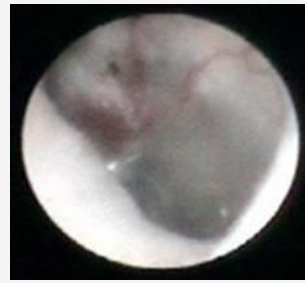| Model	Inflammation induction	Species	In vivo phase duration	Read-outs & techniques
AOM (Acute Otitis Media)	Administration of *S. pneumoniae* or *H. influenzae*	Chinchilla	10 days	• **Clinical signs, tympanometry, otoscopic scoring, tympanostomy, video recording of drug passage through tube terminal**
OME (Otitis Media with Effusion)	Administration of KLH (Keyhole Limpet Hemocyanin)	Guinea pigs	24 days	• **Bacterial quantification, quantification of inflammation, macroscopic analysis of the bulla, histopathology**

Otoscopy

Control eardrum

Inflamed eardrum

Histology

Normal cochlea

Inflammed cochlea

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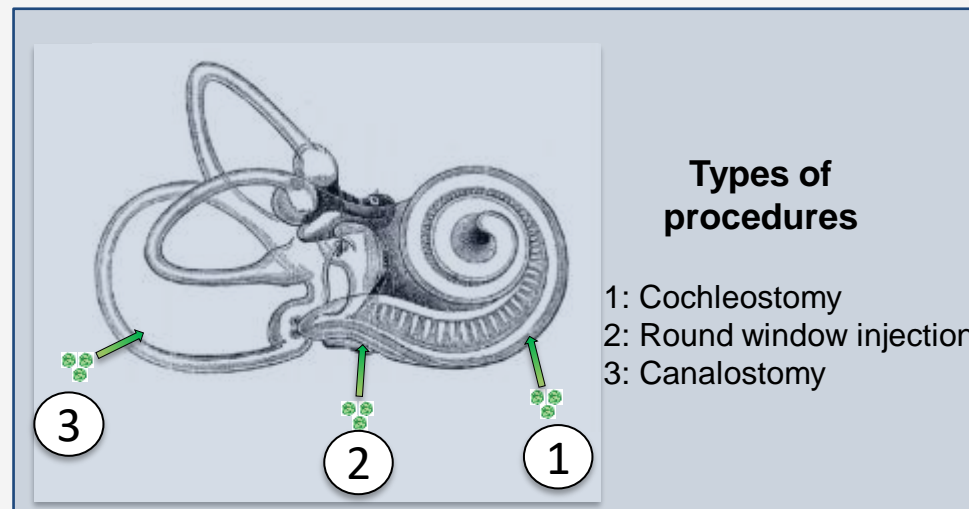
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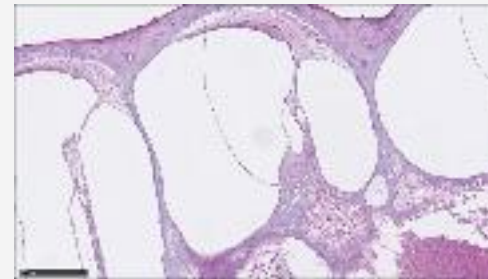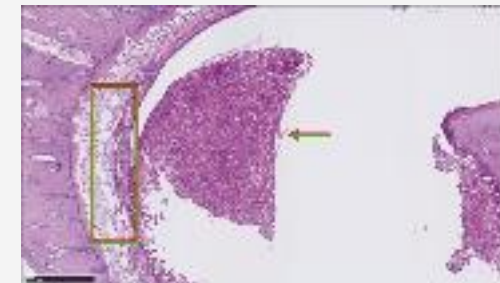
Gene Therapy animal models

Transgenic species

Routes

- Posterior semicircular canal
- Round window
- Scala media

Read-outs
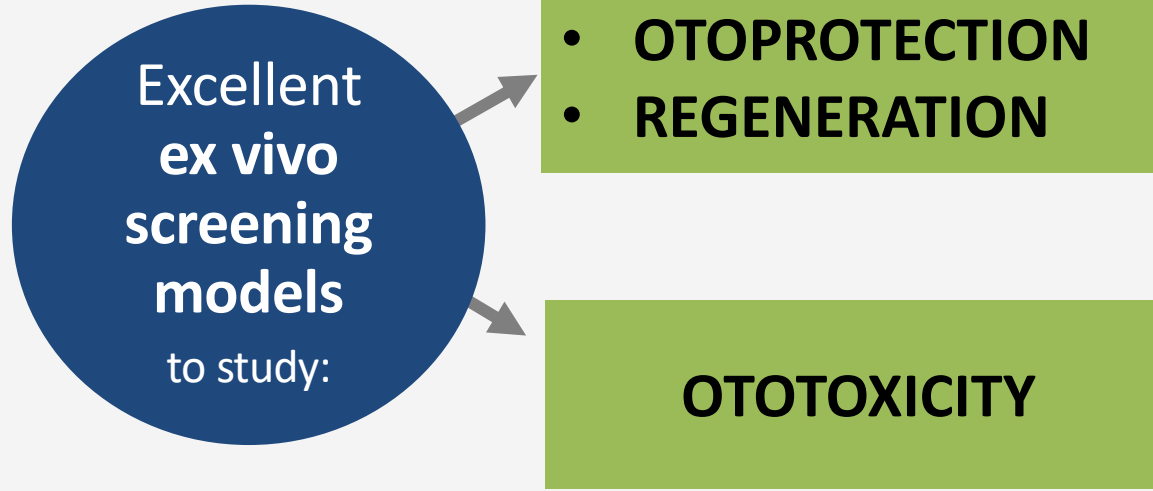
- ABR
- DPOAE
- Wave I
- Immunohistochemistry

Types of procedures

1: Cochleostomy
2: Round window injection
3: Canalostomy

Cochleostomy	Spiral ganglia	Cochlea showing transduced HC
	GFP	GFP

Injections

Species	Time of injections	
	Early post-natal	Adult
Mice	1,3	1,2,3
Rats	1,3	1,2,3
Guinea Pigs	1,3	1,3
Chinchilla	NA	1,3
Sheep	NA	1,3 *
Mini Pigs	NA	1,3 *

* Under development

Cochlear explants

Excellent ex vivo screening models to study:
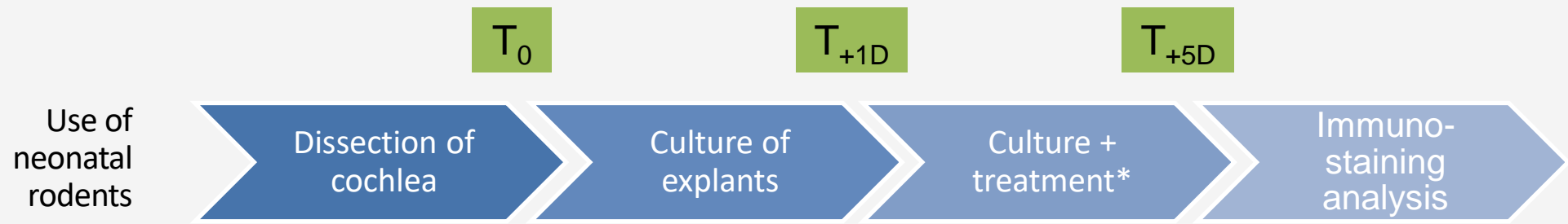
- **OTOPROTECTION**
- **REGENERATION**

OTOTOXICITY

With a wide range of read-outs:

- Hair Cell / Supporting Cell proliferation & count
- Transduction efficiency
- SGN / synapse count
- Fibrosis count
- FM143 dye uptake

- HC/SC death visualization & count
- Fibroblast count
- Hair bundle and PCP count
- Synapse and nerve count

T_0 T_{+1D} T_{+5D}

Use of neonatal rodents → Dissection of cochlea → Culture of explants → Culture + treatment* → Immuno-staining analysis

*Customized according to Sponsor protocol

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Pharmacokinetics

- Assess the availability of your compound in the inner ear & other tissues / organs

- Define dosing & treatment regimen for efficacy studies

SPECIES

Mouse, rat, guinea pig, chinchilla, gerbil, mini pig, sheep

ROUTES

Local: transtympanic, intracochlear, round window niche, intrabullar

Systemic: Intravenous / Per Os / Subcutaneous / Transdermal / Intraperitoneal

SAMPLINGS

Whole blood, plasma, perilymph, tympanic bulla, cerebralspinal fluid (CSF), brain & tissues

Tolerance studies

- Demonstrate that the drug is not ototoxic

- Define a safe dose

- Select a drug candidate

- Demonstrate that the drug is less ototoxic than the reference *(e.g. cisplatin)*

SPECIES

Mouse, rat, guinea pig, chinchilla, gerbil, mini pig, sheep

ROUTES

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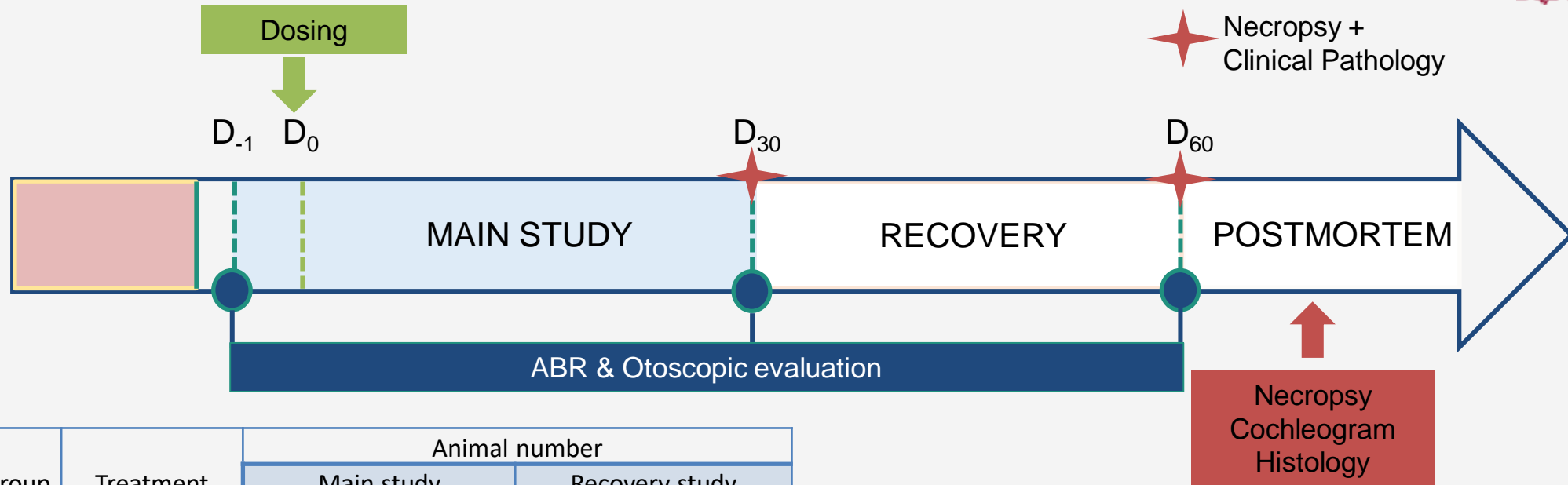
READ OUTS

Functional: ABR, DPOAE

Behavioral: GPIAS to detect tinnitus

Histology: Cochleogram

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GLP Ototoxicity studies

Dosing

Necropsy +
Clinical Pathology

D_{-1} D_0 D_{30} D_{60}

MAIN STUDY   RECOVERY   POSTMORTEM

ABR & Otoscopic evaluation

Necropsy
Cochleogram
Histology

Group	Treatment	Animal number			
		Main study		Recovery study	
		Male	Female	Male	Female
1	Control	10	10	5	5
2	Vehicle	10	10	5	5
3	Low Dose	10	10	5	5
4	High Dose	10	10	5	5
Subtotal / Gender		40	40	20	20
TOTAL		80		40	

- ✓ Route + treatment (frequency & duration) should mirror clinical use
- ✓ Vehicle toxicity also assessed
- ✓ Positive control can be used

CILcare's comprehensive range of read-outs for hearing assessments

CILcare is the best partner to support companies developing solutions for hearing disorders

- Working in the field of hearing requires a specific expertise.

- CILcare is the only CRO with this expertise.

- Our services are at the forefront of hearing research and innovation.

- Our models are carefully selected to address our clients' needs.

- We always focus on our ultimate goal : « Making Hearing a Priority »

Thank you
for your attention !

Feel free to contact me

if you wish any further information on our services

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